

## IMMUNE TOLERANCE

The immune system is precisely tuned to distinguish biochemical structures that belong to the body from those that do not, allowing it to swiftly deploy a potent array of defense mechanisms whenever evidence of a foreign invasion is found. However, disorders, including autoimmune disorders, allergic diseases, and transplant rejection, are themselves caused by inappropriate immune system responses. To fight these disorders, researchers are now building on two decades of intensive basic research in immunology to develop treatments that can induce the immune system to tolerate specific antigens. Recent progress in the development of these therapies, which have the potential to be both very potent and broadly applicable, has been very encouraging.

All tolerance-induction strategies share a common goal: to selectively prevent or diminish specific harmful immune responses without disabling the immune system as a whole. In autoimmune diseases, the idea is to make the immune system tolerant to the specific, normally occurring antigens that cause it to attack the body's own organs, tissues, or cells. In asthma and allergic diseases, the goal is to prevent responses to allergens such as cockroach and house dust mite that cause or exacerbate these diseases. For transplant rejection, the goal is to selectively block immune responses directed against the foreign antigens on the graft, and thereby allow long-term graft survival without the heightened risks of infection, malignancy, and atherosclerosis associated with current immunosuppressive therapies.

NIAID supports a wide range of research programs to turn the promise of immune tolerance therapies into reality. Many of these are administered by NIAID's Division of Allergy, Immunology, and Transplantation (DAIT), which supports basic research into the mechanisms responsible for immune tolerance, translational

research to facilitate the application of immune-tolerance approaches to human diseases, and clinical research to evaluate new therapies that can induce and maintain immune tolerance. New approaches are being investigated to

- Improve understanding of the molecular mechanisms responsible for the induction and maintenance of immune tolerance;
- Replace or improve suboptimal treatment protocols for immune-mediated diseases;
- Discover methods to prevent or reverse immune-mediated disorders for which no effective therapies are currently available;
- Create an efficient research infrastructure for the development and rapid testing of tolerogenic agents in human immune-mediated diseases; and
- Clarify mechanisms by which tolerogenic agents suppress disease.

NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the Juvenile Diabetes Research Foundation International, cosponsor the Immune Tolerance Network (ITN), an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia dedicated to the clinical evaluation of novel, tolerance-inducing therapies for autoimmune diseases, asthma and allergic diseases, and transplant rejection. ITN conducts integrated studies on the mechanisms that underlie immune tolerance and develops markers and assays to measure the induction, maintenance, and loss of tolerance in humans. The network has established several state-of-the-art core facilities and has supported 20 approved clinical protocols, as well as several additional studies of the immune mechanisms involved in tolerance. ITN is currently involved in the following areas of clinical research:

- Allergy
- Asthma
- Diabetes
- Islet cell, kidney, and liver transplantation
- Bone marrow transplantation
- Multiple sclerosis (MS)
- Psoriatic arthritis
- Systemic lupus erythematosus

Examples of active ITN clinical research studies include

- A phase I trial to analyze and monitor the safety of immunization with a fragment of the human insulin B chain in subjects newly diagnosed with type 1 diabetes; the hope is that this “autoimmunization” therapy will increase immune tolerance of insulin-producing cells.
- A pilot study to evaluate the safety and efficacy of a treatment regimen to induce tolerance in kidney transplant recipients. In this study, patients will receive low-dose steroid-free immunosuppression, two donor stem cell infusions, and an antibody called Campath-1H, which selectively eliminates immune-system T cells involved in organ rejection. Treatment will be withdrawn after 1 year and patients followed to see if long-term tolerance has been achieved.
- A phase I study in 16 patients with relapsing-remitting multiple sclerosis (MS) to assess the safety of one dose of CTLA4-IgG4m, an antibody that might block a pathway that allows the immune system to attack nervous system tissue.
- A phase II multicenter trial to evaluate the lipid-lowering drug atorvastatin in patients at high risk of developing MS.

Tolerance assays—tests and procedures to monitor patient responses to tolerance therapies—are critically needed to better evaluate tolerance-inducing therapies during and after clinical trials. ITN has therefore established a set of core laboratories to develop assays for the induction, maintenance, or loss of immune tolerance. These core facilities carry out microarray analyses of gene expression, develop analytic tools for clinical and scientific datasets from ITN-sponsored trials, and conduct enzyme-linked immunospot (ELISPOT) assay analyses of protein expression and cellular assays for T cell reactivity.

Examples of current ITN efforts to develop mechanistic assays include development of antigen-specific assays for donor-specific tolerance in kidney transplant recipients, cytokine production in children with preclinical and clinical type 1 diabetes, and identification and mechanistic investigations of tolerant kidney transplant patients. More information on ITN’s mission and research is available at [www.immunetolerance.org](http://www.immunetolerance.org).

In collaboration with NIDDK, DAIT supports the Nonhuman Primate Transplant Tolerance Cooperative Study Group. The goal of this program is to evaluate the safety and efficacy of novel tolerogenic regimens in preclinical models of kidney and islet transplantation. Scientists in this study group have demonstrated long-term graft acceptance using tolerogenic regimens in both kidney and islet allograft recipients. In FY 2005, the program expanded the scope of transplantation models to include nonhuman primate models of heart and lung transplantation, and to provide an opportunity for critical preclinical research to complement NIAID-supported transplantation clinical trials. The program’s previous expansion allowed the sharing of valuable resources and facilitated the development of new collaborations. To accelerate research conducted through this program, DAIT

maintains breeding colonies of specific pathogen-free rhesus and cynomolgus macaques.

Other DAIT-supported research programs that include studies on immune tolerance are the Autoimmunity Centers of Excellence, Innovative Grants on Immune Tolerance, and program projects in basic biology, basic immunology, and transplantation tolerance. The goals of these projects are to (1) determine the molecular

mechanisms by which cells of the immune system are rendered unresponsive, (2) develop experimental models of tolerance induction, and (3) evaluate tolerance induction strategies in animal models of transplantation or autoimmune diseases. The knowledge gained from these program projects will accelerate the development of clinical strategies for tolerance induction in immune-mediated diseases.